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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/675,927	09/29/2003	Payman Amiri	18773.004	2378

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EXAMINER	
KANTAMNENI, SHOBHA	
ART UNIT	PAPER NUMBER
1617	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/675,927	AMIRI ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *75,76,78,80,82,83,87-106 and 108-111* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *75-76,78,80,82-83,87-106,108-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 12/03/2007, wherein claims 87-88, 90-91, 93, 96, 99-101, and 104-106 have been amended.

Upon further consideration, the rejection of claims 75-76, 78, 80, 82, 83, and 87-106, 108 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is herein withdrawn.

Applicant's arguments have been considered, but not found persuasive. The rejection of claims 75, 76, 78, 80, 108 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is MAINTAINED. See under response to arguments.

Applicant's arguments have been considered, but not found persuasive. The rejection of claims 82, 83, 87-106, 109-111 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating some particular/specific cancer disorders in a human or animal comprising administering a composition comprising instant compounds represented by formula (I), does not reasonably provide enablement for treating any cancer disorder as in claim 82 mediated by Ras mitogen activated protein kinase pathway is MAINTAINED. See under response to arguments.

Claims 75, 76, 78, 80, 82, 83, 87-106, 108-111 are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 75, 76, 78, 80, 108 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. See the discussion below.

Claims 82, 83, 87-106, 109-111 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating some particular/specific cancer disorders in a human or animal comprising administering a composition comprising instant compounds represented by formula (I), does not reasonably provide enablement for treating any cancer disorder as in claim 82 mediated by Ras mitogen activated protein kinase pathway. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without **undue experimentation**. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of

the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of treating a cancer disorder in a human or animal subject, comprising administering a composition comprising a compound represented by formula (I). The nature of the invention is complex in that it encompasses the treatment of any type of cancers as in claim 75, and types of cancer as in claims 78 and 82 mediated by Ras/mitogen activated protein kinase pathway.

(2). Breadth of the Claims:

The complex nature of the subject matter of this invention is greatly exacerbated by the breadth of the claims. The claims encompass treatment of a number of cancers as in claim 75, and cancers mediated by Ras/mitogen activated protein kinase pathway as in claims 78 and 82, comprising administering a composition comprising a compound represented by formula (I). What's more, the scope of the compounds claimed to be useful for the treatment of cancer is extremely broad. The instant claims are deemed very broad since these claims read on a method of treatment of any cancer by inhibiting Raf kinase activity.

(3). Guidance of the Specification / (4). Working Examples:

The specification does not provide any guidance as to how one would administer the claimed compositions comprising instant compounds to a subject and treat **any** type of cancer cell.

All of the guidance provided by the specification is directed towards the synthesis of the compounds represented by formula (I). Applicant provides in the specification on pages 307-309 *in vitro* assay protocol, Raf Screening in general. The specification discloses on page 309 "Using the procedures of Examples 1401 or 1402, the compounds of Examples 1-1094 were shown to have a raf kinase inhibitory activity at an IC_{50} of less than 50 μM."

There are no working examples for the treatment of cancer using a composition comprising compounds of Formula (I).

(5). State of the Art:

While the state of the art is relatively high with regard to treating specific cancers in general, and specific cancers mediated by Ras/mitogen-activated protein kinase signal pathway, the state of the art with regard to treating any cancer disorder is underdeveloped. In particular, there is no known anticancer agent which is effective against all cancers. Carter, et al. (Chemotherapy of Cancer, 2nd ed., 1981) clearly teaches that for the forty known anticancer agents, none are effective against all cancers (pages 362-365). There are compounds that treat a range of cancers, but no one has ever been able to figure out how to get a compound to be effective against cancer generally, or even a majority of cancers. Thus, the existence of such a "silver bullet" is contrary to our present understanding in oncology. This is true in part because cancers arise from a wide variety of sources, such as viruses (e.g. EBV, HHV-8, and HTLV-I), exposure to chemicals such as tobacco tars, genetic disorders, ionizing radiation, and a wide variety of failures of the body's cell growth regulatory mechanisms.

Different types of cancers affect different organs and have different methods of growth and harm to the body, and different vulnerabilities. Even those that affect a single organ are often not generally treatable. For example, the main types of lung cancer are small cell (oat cell), giant cell, clear cell, adenocarcinoma of the lung, squamous cell cancer of the lung, and mesothelioma. There is no such thing as a treatment of these generally because of their diversity. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally, evidence that the level of skill in this art is low relative to the difficulty of such a task.

(6). Predictability of the Art:

The invention is directed to treatment of cancer as in claim 75, and cancers as in claims 78, and 82 mediated by Ras/mitogen-actived protein kinase signal pathway by administering a composition comprising a compound of formula (I).

It is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). Cancers are especially unpredictable due to their complex nature. Please refer to the discussion of Carter, et al. and the state of the art in (5) that shows the different treatments of cancers. The treatment of one type of cancer could not be necessarily the same for the other type. Further, Rowinsky et al. (Journal of Clinical Oncology, Vol 17, No.11, 1999, pages 3631-3652) teaches that "the animal tumor models used to evaluate FTase inhibitors do not fully recapitulate the complexity of genetic alterations in human tumors", and also teaches that mutated ras alone is but one genetic lesion

essential for the complete conversion of a normal cell to the fully malignant phenotype raises the question of whether approaches to correct the ras defect alone will have any significant antitumor activity. It is also taught that there is limited experimental evidence to suggest that correlation of just a single defect, such as ras mutation, can significantly impair the aberrant growth of tumor cells. See page 3647, paragraphs 1-2 under summary. Thus, the instant claimed invention as discussed above is **highly unpredictable**.

The applicant has not provided any competent evidence that the instantly disclosed tests are highly predictive for any or all types of cancers disclosed and embraced by the claim language for the intended host. Lack of a working example is a critical and crucial factor to be considered, especially in a case involving an unpredictable and undeveloped art. See MPEP 2164. As discussed above, treatment of cancer as in claim 75, and any cancers as in claims 78, and 82 mediated by Ras/mitogen-actived protein kinase signal pathway by administering a composition comprising a compound of formula (I) is highly unpredictable.

Moreover, the standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court of Mineral Separation v. Hyde, 242 U.S. 262, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied.

(7). The Quantity of Experimentation Necessary:

In order to practice the claimed invention, one of skill in the art would have to first envision a compound, a dosage for each compound, an appropriate pharmaceutical carrier, the duration of treatment, route of treatment, etc. and, in the case of human treatment, an appropriate animal model system for one of the claimed compounds. One would then need to test the compound in the model system to determine whether or not the compound is effective for inhibiting Raf kinase acitivity, and determine whether or not the compound is effective in treating a specific type of cancer cells. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regarding treatment of cancer with any compound, one of skill in the art would have to then either envision a modification of the first pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, and test the system again. In order to practice Applicant's invention, it would be necessary for one to conduct the preceding experimentation for each type of cancer because, as described by Carter, et al., there is no known drug effective for treating all types of cancer. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to treat any cancer disorder as in claim 75, and those cancer disorders mediated by Ras/mitogen-activated protein kinase signal pathway in a human or animal subject by administration a composition comprising one of the compounds represented by formulas (I).

As discussed above, mutated ras alone is but one genetic lesion essential for the complete conversion of a normal cell to the fully malignant phenotype, every cancer disorder has its unique chemical pathway of expression, diagnosis and treatment of

individual cancer and condition cannot be predicted a priori but must be determined from case to case by painstaking experimental study and when the above factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine which compounds of Formula I treats which cancer diseases. Furthermore, chemical modification of biomolecules may alter the biological property that is important in the use of that particular, and also other properties such as solubilities in aqueous media, binding affinities etc. Thus variety of compounds encompassed by formula (I) will have different biological properties. Considering variety of compounds covered by Formula I and the multitude of different cancer diseases to be treated, this is a very large degree of experimentation.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, a method for treating any cancer or all types of cancers as in claim 75, and those cancer disorders mediated by Ras mitogen activated protein kinase pathway as in claims 78, 82 by administering the various compounds represented by formula (I) is not considered to be enabled by the instant specification.

Response to Applicant's Arguments:

Applicant's arguments have been considered, but not found persuasive.

It is pointed out that in order to practice Applicant's invention, it would be necessary for one to conduct experimentation for each type of cancer as in claim 75,

78, and as in claim 82 because as described by Carter et al., there is no known drug effective for treating all types of cancer. Further, it is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970). Cancers are especially unpredictable due to their complex nature. Please refer to the discussion of Carter, et al. and the state of the art in (5) that shows the different treatments of cancers. The treatment of one type of cancer could not be necessarily the same for the other type. Further, Rowinsky et al. (Journal of Clinical Oncology, Vol 17, No.11, 1999, pages 3631-3652) teaches that "the animal tumor models used to evaluate FTase inhibitors do not fully recapitulate the complexity of genetic alterations in human tumors", and also teaches that mutated ras alone is but one genetic lesion essential for the complete conversion of a normal cell to the fully malignant phenotype raises the question of whether approaches to correct the ras defect alone will have any significant antitumor activity. It is also taught that there is limited experimental evidence to suggest that correlation of just a single defect, such as ras mutation, can significantly impair the aberrant growth of tumor cells. See page 3647, paragraphs 1-2 under summary. Thus, the instant claimed invention as discussed above is **highly unpredictable**.

The applicant has not provided any competent evidence that the instantly disclosed tests are highly predictive for any or all types of cancers disclosed and embraced by the claim language for the intended host. Lack of a working example is a critical and crucial factor to be considered, especially in a case involving an

unpredictable and undeveloped art. See MPEP 2164. As discussed above, treatment of cancer as in claim 75, and any cancers as in claims 78, and 82 mediated by Ras/mitogen-actived protein kinase signal pathway by administering a composition comprising a compound of formula (I) is highly unpredictable.

Therefore, a method for treating any cancer or all types of cancers as in claim 75, and those cancer disorders mediated by Ras mitogen activated protein kinase pathway as in claims 78, 82 by administering the various compounds represented by formula (I) is not considered to be enabled by the instant specification.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period, will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Tuesday, Thursday-Friday, 8am-4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, Ph.D can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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